PATENT
Docket No. 9425/46701

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor: Samuel BOGOCH

Serial No.: 08/031,562

Filing Date: March 16, 1993

For: RECOGNIN VACCINES

Art Unit: 1813

Examiner: J. Krsek
Staples

Commissioner of Patents
and Trademarks
Washington D.C. 20231

SUBMISSION OF APPELLANT'S BRIEF UNDER 37 C.F.R. §1.192

Sir:

Submitted herewith please find an original and two copies of Appellant's Brief on Appeal. Kindly charge the statutory fee of $140.000 to Kenyon & Kenyon Deposit Account No. 11-0600. Authorization is also hereby given to charge any additional fees under 37 C.F.R. §1.116 OR §1.117 or to credit any overpayment to said deposit account.

Date: July 17, 1995

Respectfully submitted,
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APPEAL BRIEF UNDER 37CFR §1.192

Sir:

This is Appellant's Brief under 37 CFR §1.192 pursuant to the Notice of Appeal filed under 37 CFR §1.191 on March 13, 1995 and received at the U.S. Patent and Trademark Office on March 15, 1995. This appeal is taken with respect to claims 1 and 2 shown in the Appendix.

(1) Status of Claims

The Notice of Appeal filed March 13, 1995 was taken with regard to claims 1 and 2.

(2) Status of Amendment

No amendments to the claims were made after Final Rejection.

(3) Summary of Invention

The invention defined in the claims involved in this appeal is, in one aspect, concerned with a method of treating or preventing the growth of cancer cells in

a patient (claim 1). In the broadest definition of this invention, as set forth in claim 1, the method comprises administering to a patient a vaccine composed of malignin, Recognin L, Recognin M or other Recognin or derivative thereof which exhibits immunologic specifity in the form of eliciting an anti-Recognin antibody response.

In a second aspect, as defined by claim 2, the vaccine is an agent having the immunological specificity of malignin, Recognin L or Recognin M, which, when administered to a patient inhibits the growth of cancer cells, thereby preventing cancer or if administered to a patient suffering from cancer, will inhibit the further growth of or destroy cancer cells.

The present invention is based, in part, on the discovery that antibodies to certain tumor markers exist in non-tumor bearing individuals and increase in concentration in a temporal manner as the risk of cancer increases with age (page 5, lines 11-15). Specifically, antibodies to malignin and Recognin polypeptides, which are immunologically closely related cancer cell antigens, can be detected in non-tumor bearing individuals and increase in concentration with age in healthy non-tumor bearing individuals between the third and seventh decades as the risk of cancer increases (page 5, lines 11-16). Higher concentrations of antimalignin antibodies have been demonstrated to correlate with long term survival of cancer patients (page 3, lines 23-26). Moreover, antibodies to malignin and Recognin were discovered to be cytotoxic or at least cytostatic to cancer cells at picogram concentrations per cell (Example 6 at page 12).

Various tumor associated substances, oncoproteins and tumor antigens have been identified. However, no known tumor associated substance has heretofore been shown to elicit an immune response that is specific to

cancer cells and which is cytotoxic or cytostatic to cancer cells in general (page 5, lines 1-3).

Current efforts to control cancer through immunological manipulations include the use of various antigenic peptides directed to specific cancer cell markers, i.e. cancer vaccines. Many peptide antigens have been tested in vitro and have demonstrated cytotoxicity toward their target cancer cells. Phase I clinical trials of many of these peptide vaccines have borne out the cytoxity observed in vitro (Cancer Vaccines, Abstracts of the Cancer Research Institute Symposium on Cancer Vaccines, 1994, at Abstract SO5 and SO6, of record). Although the absolute requirements for maximum protection are not yet known, these studies demonstrate that cancer peptide vaccines can confer some immunologic benefit to some patients.

Although various peptide cancer vaccines are known, (See Cancer Vaccines) none of these vaccines induces an immunological response specifically to malignant cells. The present vaccine differs from other cancer vaccines in that the immunological peptide used in the present vaccine elicits production of antibodies that specifically recognize various types of malignant cells, the antibodies being antibodies that are found to be naturally produced in humans. There is a strong correlation between the level of the naturally occurring anti-malignin antibodies and the natural biological risk of cancer, which increases with age. Moreover, these anti-malignin antibodies can be detected in individuals who have no detectable cancer (Neurochemistry and Clinical Neurology, ed. by Alan Liss, Inc., N.Y., N.Y., 407-424).

The present cancer vaccine and method induce and enhance a natural response to cancer cell antigens, regardless of the type and origin of the cancer. Anti-Recognin antibodies, which are produced in response to the peptide vaccine of the present invention have been shown to attach to various malignant cells, including for example, squamous cell carcinoma cells, retrobulbar malignant neuroectodermal cells, and lymphoma cells (Figure 1).
These antibodies have cytotoxic effect upon their target cells and inhibit the growth of various cancer cell in vitro (Figure 2).

(4) Issues

The issue presented in this appeal is whether the invention set forth in claims 1 and 2, which are directed to a process and vaccine, respectively, for inhibiting the growth of or destroying cancer cells in a patient, is enabled by the specification, within the meaning of 35 USC §112, first paragraph.

(5) Grouping of Claims

For purposes of this appeal, claim 1 will stand or fall as a first group, and claim 2 will constitute a second group, each of these groupings being separately and independently patentable.

(6) Argument

Claim 1, directed to a process for inhibiting the growth of or destroying cancer cells in a patient is fully enabled by the specification, since the specification teaches how to make and administer the

cancer inhibiting/destroying agent to a patient in need thereof. The cancer inhibiting/destroying agent of the invention is defined as a peptide having the immunological specificity of malignin, Recognin L or Recognin M, which are cancer cell surface antigens present on various types of cancer cells. In Example 8, at pages 17 through 18 of the specification, it is disclosed that an antigenic peptide of malignin, Recognin L or Recognin M is administered subcutaneously to a patient at a dosage of about 1 mg or more. It is further disclosed that after the initial inoculation booster shots may be administered at 10 and 20 days post initial inoculation. Additional booster shots of the vaccine may be administered to the patient in order to maintain increased levels of anti-Recognin antibody which occur at about 10 days post inoculation; the level of antibody being monitored by art-recognized methods throughout the course of treatment. It is further disclosed in Example 8 that in the case where the vaccine is administered to a patient suffering from clinically diagnosed cancer, clinical determinations, such as CATSCAN, magnetic resonance imaging (MRI), and blood count may be utilized to determine the appropriate treatment regimen.

Thus, Appellant has clearly taught how to practice the invention as set forth in claim 1. The person of ordinary skill in the art need only follow the steps provided in the application.

Claim 2, which is directed to a vaccine for the treatment or prevention of cancer is also described in Example 8 at pages 17 to 18. It is disclosed that the vaccine is a product that may be a biologically functional derivative of malignin, Recognin L or

Recognin M having the immunological specificity thereof. It is also disclosed that the antigenic peptide vaccine may be produced synthetically or by cell or tissue purification procedure. Further details concerning the art known methods of synthesizing or purifying the peptide vaccine are provided in Appellant's co-pending application Ser. No. 07/744,649, which was incorporated into the present specification by reference. As such, the present specification provides an enabling disclosure for making and using the claimed vaccine.

It is respectfully submitted that Appellant's teachings "of the manner and process of making and using the invention in terms which correspond in scope to those used in defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of § 112 unless there is reason to doubt the objective truths of the statements contained therein which must be relied on for enabling support." In Re Marzocchi & Horton, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971). See also In Re Dinh-Nguyen and Sterhagen, 181 U.S.P.Q. 46 (C.C.P.A. 1974) and In Re Bowen, 181 U.S.P.Q. 48 (U.S.P.Q. 1974).

The basis of the Examiner's rejection is not that Applicant has not described how to practice the claimed method (claim 1) or how to make and use the claimed vaccine (claim 2), but rather that the Examiner doubts that use of the claimed method or vaccine will provide protective immunity when administered in vivo. That is, the Examiner has couched a utility rejection in the language of §112. However, the Examiner has provided no evidence to support doubts of the objective truth of the disclosure or conjecture that the claimed invention will

fail to provide any protective immunity when practiced according to claim 1 or claim 2.

It is respectfully submitted that Appellant has provided sufficient evidence of the effect of anti-Recognin antibody on tumor growth and the ability of anti-Recognin antibody to provide some protective immunity. For example, Appellant has provided data that demonstrate that anti-Recognin antibody level increases in an individual harboring a tumor and increases during tumor growth in an individual but is significantly reduced upon surgical removal of the tumor or after treatment to reduce the tumor size (page 15, lines 18 through 27 and Figure 3). Actuarial data, calculated at probability levels below $p < 0.0001$, that correlate the length of survival of clinically diagnosed cancer patients with serum level of anti-Recognin antibody have also been provided (See Bogoch, et al., Cancer Detection and Prevention, 12: 312-320 (1988), of record).

The Examiner objected to the actuarial data, citing a reference (Biostatistical Analysis, ed. by Zar, Prentice-Hall, Inc.) in rebuttal of Appellant's data. However, the cited reference actually bolsters Appellant's position concerning the actuarial data. It is stated that "equations may inaccurately represent natural processes yet may be employed advantageously to predict the value of one variable given the value of an association variable." Id. at 27B. Thus, even if the actuarial data does not demonstrate a direct relationship between anti-Recognin antibody level and long term survival to cancer, it is an indicator of a role for anti-Recognin antibody in defending against malignancies.

Moreover, Appellant is not merely relying on the actuarial data, but has provided further evidence of the effects of the present method and vaccine on cancer cell growth. Appellant has provided in vivo data obtained from use of an art accepted animal model of cancer that demonstrate the ability of anti-Recognin antibody to bind preferentially to malignant cells present in mouse brain when said antibodies are administered intravenously (Bogach, et al., Protides of Biological Fluids, 30: 337-352 (1983), of record). In vitro data showing the effect of anti-Recognin on cancer cells is also provided in Figure 2, wherein the growth inhibition properties of the claimed vaccine are demonstrated, i.e. anti-Recognin antibody inhibits the growth of small cell lung carcinoma cells at picogram concentrations. It is noteworthy that the ability of monoclonal antibodies to inhibit target cells usually requires use of significantly higher concentrations of antibody, e.g. milligrams or at least microgram amounts. Thus, the present vaccine is not only effective, but is effective at significantly lower concentrations than would be expected.

Furthermore, the data presented in Figure 1 and Figure 2 demonstrate the cytotoxicity and growth inhibition properties, respectively, of anti-Recognin antibody to various malignant cells.

It is respectfully submitted that the totality of the evidence establishes that anti-Recognin antibodies elicit protective immunity against cancer. Based on the data as a whole, one of ordinary skill in the art would conclude that anti-Recognin antibodies provide some protective immunity to cancer and that the claimed method of treating or preventing cancer and the claimed

peptide vaccine which has the immunological specificity of malignin or Recognin, i.e., elicits anti-malignin antibodies, are useful in the treatment and prevention of cancer.

It is further submitted that the specification teaches how to make and use the vaccine of claim 2 and how to practice the method of claim 1.

Accordingly, the final objection to the specification and rejection of claims 1 and 2 as allegedly failing to provide an enabling disclosure should not be affirmed. The Honorable Board of Patent Appeal and Interferences should find that the Examiner erred in finally rejecting claims 1 and 2 under 35 USC §112, first paragraph.

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